REMARKS

Reconsideration is requested.

The interview of October 28, 2008 with Examiner Gussow and Examiner Blanchard is acknowledged, with appreciation. The Examiner's Interview Summary is accurate in it's brief description of the issues discussed. Further comments from the undersigned's recollection of the interview are provided herein.

The above amendment of claim 17 is believed to obviate the Section 112, second paragraph, rejection of claims 17-20, 23-26, 31 and 33-35. The above amendment of claim 17 was discussed with the Examiners during the interview and the undersigned is of the understanding that the Examiners agreed that the amendment would obviate the Section 112, second paragraph, rejection.

The applicants submit that one of ordinary skill will appreciate from the unamended claims that "anti-PTHrP (34-53) antibody" refers to an antibody that binds residues 34-53 of PTHrP. The Examiner is requested to see the following, copies of which are being filed concurrently herewith:

(1) Okada et al "Immunohistochemical Localization of Parathyroid Hormone-related Protein in Canine Mammary Tumors" Vet Pathol **34**: 356-359 (1997) (describing an antibody to "PTHrP (1-36)" (page 356 right column), the use of a "commercially available rabbit-derived anti-PTHrP (34-53) antibody" (id..), and the N-terminus (1-36) and midregion (36-111) of PTHrP);

(2) Verheijen et al, "Parathyroid hormone-related peptide (PTHrP) induces parietal endoderm formation exclusively via the Type I PTH//PTHrP receptor"

Mechanisms of Development 81 (1999) 151-161 (describing the N-terminus of PTHrP as "PTHrP (1-34)" (see page 151, left column), the use of the N-terminal fragment "PTHrP(1-34)" and full length version "PTHrP(1-141)" (see page 152, right column), and fragments spanning amino acids 67-86, 67-94 and 107-139 as "PTHrP(67-86)", PTHrP(67-94)" and "PTHrP(107-139)", respectively (see page 153, left column and Figure 1, and the "Materials" section on page 158 which describes the source of peptides and antibodies));

(3) Thorikay et al., "Synthesis of a gene encoding parathyroid hormone-like protein-(1-141): purification and biological characterization of the expressed protein" Endocrinology, Vol 124, 111-118 (1989) (abstract) (describing "PTHLP" as a 141 amino acid protein designated "PTHLP-(1-141)");

(4) Fenton et al., "A carboxyl-terminal peptide from the parathyroid hormone-related protein inhibits bone resorption by osteoclasts." Endocrinology. 1991 Oct;129(4):1762-8 (Abstract) (describing a carboxy fragment of PTHrP as "PTHrP-(107-139)");

(5) Santos et al "Up-regulation of parathyroid hormone-related protein in folic acid-induced acute renal failure" Kidney International, vol. 60 (2001), pp 982-995 (describing "anti-PTHRP antibody Ab-2 (Oncogene, Uniondale, NY, USA), [as] recognizing the sequence 34 to 53 of human and rat PTHrP" on page 983);

(6) Garcia-Ocana et al "Cyclosporine increases renal parathyroid hormone-related protein expression in vivo in the rat" transplantation, vol 65, 860-863, No. 6,

March 27, 1998 (describing "anti-PTHRP antibody Ab-2 (Oncogene, Uniondale, NY), [as] recognizing the sequence (34-53) of human and rat PTHrP" on page 861); and

(7) Richard, et al. "Humoral Hypercalcemia of Malignancy, Severe Combined Immunodeficient/Beige Mouse Model of Adult T-Cell Lymphoma Independent of Human T-Cell Lymphotropic Virus Type-1 Tax Expression" Am J Pathol. 2001 June; 158(6): 2219–2228 (describing "polyclonal rabbit anti-PTHrP (PTHrP amino acids 34 to 53) (1:100, Ab-2, Oncogene Research Products, Cambridge, MA)").

Each of the above-noted references describes fragments of PTHrP by the amino acid positions, in parentheses, in a manner similar to the applicants disclosure and claims.

The following references, for example, already of record make similar reference to fragments of PTHrP:

(A) Burtonet al., "Parathyroid hormone related peptide can function as an autocrine growth factor in human renal cell carcinoma" 1990, Biochemical and Biophysical Research Communications, Vol. 167, No. 3, pages 1134-1138;

(B) Ogata et al (EP1197225);

(C) Hoare et al "Specificity and stability of a new PTH1 receptor antagonist, mouse TIP(7-39)" Peptides, 2002, vol 23, No. 5, pp 989-998; and

(D) Sato et al (U.S. Patent No. 6,903,194).

Sato et al describes "Humanized anti-PTHrP (1-34) Antibody" in Figures 13 and 14. Moreover, Sato et al describes the use of a fragment "[PTHrP(1-34)]" as an antigen to produce antibodies as follows:

> "PTHrP used for the immunization of animals includes peptides having the whole or part of the amino acid sequence of PTHrP prepared by recombinant DNA technology or chemical synthesis, and PTHrP derived from supernatants of cancer cells causing hypercalcemia. For example, a peptide [PTHrP(1-34)] comprising the 1st to 34th amino acids of the known PTHrP (Kemp, B. E. et al., Science (1987) 238, 1568-1570) may be used as the antigen." See column 7, lines 48-55 of Sato.

Further, Sato describes antibodies binding human PTHrP as "anti-human PTHrP antibodies" and generally antibodies which bind PTHrP as "Anti-PTHrP Antibody". See column 10, last line, column 22, line 56, and, for example, column 23, lines 25 and 37-38 of Sato.

One of ordinary skill in the art will appreciate that "an anti-PTHrP (34-53) antibody" is a general recitation of an antibody which binds to the fragment of PTHrP spanning amino acids 34-53.

The present specification describes the following as examples of an anti-PTHrP antibody which may be an antagonist according the disclosed invention: the anti-PTHrP(1-34) antibodies (human, rat) of Bachem (Bachem Biochimie Sarl, Voisins-le-Bretonneux, France), the anti-PTHrP(34-53) antibody (Ab-2, human) of Oncogene (France Biochem, Meudon, France), the antibody #23-57-137-1 (described in particular in the patent application EP1197225) and the anti-PTHrP(107-139) antibody (human) obtained by conventional methods of antibody preparation. See page 9, lines 10-15 of the present specification. One of ordinary skill in the art will further appreciate from, for example, page 21, line 31 ("anti-PTHrP (34-53)"), page 17, lines 25-28 ("The anti-PTHrP(34-53) antibody (Ab-2, human) was obtained from Oncogene (France Biochem,

Meudonm France) and the anti-PTHrP(107-139) antibody (human) was a gift of Dr. P. Esbrit (Fundacion, Jimenez Diaz, Madrid, Spain)") and page 27, line 1 ("Int. region: anti-PTHrP (34-53) antibody (Ab-2, Oncogene) 2 μg/ml") of the specification, that the present specification describes the use of anti-PTHrP antibodies from a number of sources as exemplifications of anti-PTHrP antibodies which bind to the amino acid fragment described numerically in parentheses (i.e., fragments of PTHrP spanning amino acids 34-53 and 107-139 in the above-noted passages).

As noted above, the claims have been amended, without prejudice, in a manner believed to obviate the Section 112, second paragraph, rejection based on the interview with the Examiner and the Examiner's Supervisor.

Withdrawal of the Section 112, second paragraph, rejection is requested.

The Section 112, first paragraph "written description" rejection of claims 17-20, 23-26, 31 and 33-35 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following.

The Examiner is understood to be of the view that the present disclosure provides a written description for a "genus" of anti-PTHrP antibodies and a specific species of the "subgenus" of the anti-PTHrP antibodies of the claims, without describing the subgenus of the claims. The Examiner is further understood to believe that the specification only describes a commercially available species of the claimed "subgenus", i.e., Ab-2 from Oncogene (which is believed to now be available from CALBIOCHEM EMD Chemicals under the name "Anti-PTHLP (Ab-2) (34-53) Rabbit pAb"). The Examiner relies on In re Smith 173 USPQ 679 (CCPA 1972) for the

assertion that "It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads." See page 4 of the Office Action dated August 1, 2008.

The Examiner is believed to have agreed during the interview that the specification teaches a peptide fragment of PTHrP spanning amino acids 34-53 as an antigen to which an anti-PTHrP antibody can be made to bind. The Examiner is believed to have agreed during the interview that an antibody which binds to a fragment of PTHrP spanning amino acids 34-53 would be reasonably referred to as an anti-PTHrP (34-53) antibody. The Examiner is believed to have agreed during the interview that the specification, taken with the generally advanced level of skill in the art, teaches one of ordinary skill in the art how to make and use an anti-PTHrP (34-53) antibody according to the claimed invention. The applicants note the previously-filed Declaration of MASSFELDER executed February 14, 2008 in this regard.

The Examiner believes however that the specification fails to describe the claimed method wherein the PTHrP antagonist is an anti-PTHrP (34-53) antibody.

The present specification describes in the background section the previous experiences in the art with anti-PTHrP antibodies and that the present application provides a therapy based on the use of PTHrP antagonists to treat patients affected by clear cell carcinoma (CCC). See page 5, last paragraph of the specification. (i.e., invention of the application . PTHrP antagonists are described in specification as including compounds which decrease the biological effect or effects of PTHrP and can include a compound binding the PTHrP receptor which partially or wholly inhibits

binding of PTHrP to its receptor. These antagonists of the invention are described as including peptides of PTH or PTHrP comprising a substitution or deletion of at least one amino acid of the sequence of the PTH and or the PTHrP, or a partial sequence of the PTH or PTHrP peptides, optionally comprising a substitution or a deletion of at least one amino acid of their sequence. See page 7, lines 3-14 of the specification.

The specification further describes that specific examples of antagonist compounds binding the PTHrP receptors according to the invention include PTHrP (3-34), PTHrP (7-34), PTHrP (8-34), PTHrP (9-34), PTHrP (10-34), the amides or variants thereof. Variants present a replacement, a deletion or an addition of at least one amino acid such as in particular (Asn10, Leu11, D-Trp12) PTHrP (7-34) amide (human or murine). One of ordinary skill in the art will appreciate that "PTHrP(3-34)", for example, is a peptide containing the amino acid sequence of amino acids 3 to 34 of the PTHrP peptide. The specification further describes that among the above-described polypeptides, are also included those which present a deletion, a substitution, an addition or an insertion of at least one amino acid of the peptide sequence of PTH or PTHrP and which have an antagonist activity in respect of PTHrP. The specification further describes a derivative of TIP (tuberoinfundibular peptide) as a PTHrP antagonist, such as truncated peptides of TIP(1-39) (tuberoinfundibular peptide 1-39), in particular TIP(7-39) and its derivatives which have been described as powerful RPTH1 antagonists (Hoare et al, Peptides 23 : 989-998, 2002). See page 7, lines 14-26 of the specification.

The specification further describes that the PTHrP antagonist according to the invention may be a non-peptidic compound. See page 7, lines 27-29 of the specification.

The specification describes that a PTHrP antagonist according to the invention can be a compound binding a ligand of the PTHrP receptor, thereby partially or even totally inhibiting the binding of PTHrP to its receptor. This compound can be selected from anti-PTHrP antibodies and, more preferably, a humanised anti-PTHrP antibody. See page 7, lines 30-33 of the specification.

The specification describes that a PTHrP antagonist according to the invention can be a compound increasing the presence of active VHL, thereby decreasing the biological effect or effects of PTHrP, such as a product of the tumour suppressing gene VHL, which can be obtained in particular by gene therapy. The specification further describes that a PTHrP antagonist according to the invention can be a compound reducing the expression of PTHrP. This compound can bind mRNA or the gene of PTHrP, inhibiting, partially or even totally the expression of PTHrP. This compound can be for example an antisense oligonucleotide of PTHrp, a RNAi, a transcription factor repressing the expression of the PTHrP gene or a compound decreasing the stability of the mRNA of PTHrP. See page 8, lines 1-11 of the specification.

The present invention also includes the possibility of using several kinds of PTHrP antagonists such as defined throughout the specification for the treatment of kidney cancer. The specification describes, for example, a method of treatment including gene therapy and the administration of a PTHrP antagonist such as an

antagonist of the PTHrP receptor or an anti-PTHrP antibody. See page 8, lines 12-17 of the specification.

Antagonists are further described in the specification as including a compound, such as an anti-PTHrP antibody, which inhibits the binding of a ligand, such as PTHrP, to a PTHrP receptor. Examples of anti-PTHrP antibodies include antibodies such as a humanised antibody, a human antibody, a chimeric antibody, an antibody (such as the antibody #23-57-137-1 (which binds PTHrP(1-35) see attached Esaki et al "The selection of therapeutic antibodies by kenetic analysis" Biocore Journal – Number 2 2002, pages 7-8)) obtained from a hybridoma (such as the hybridoma #23-57-137-1) or a fragment of an anti-PTHrP which inhibits binding of a ligand to the receptor and/or a modified form of such a fragment. The antibody can be polyclonal or monoclonal. See page 8, lines 23-31 and page 9, lines 4-9 of the specification.

The present specification describes the following as examples of an anti-PTHrP antibody which may be an antagonist according the disclosed invention: the anti-PTHrP(1-34) antibodies (human, rat) of Bachem (Bachem Biochimie Sarl, Voisins-le-Bretonneux, France), the anti-PTHrP(34-53) antibody (Ab-2, human) of Oncogene (France Biochem, Meudon, France), the antibody #23-57-137-1 (described in particular in the patent application EP1197225) and the anti-PTHrP(107-139) antibody (human) obtained by conventional methods of antibody preparation. See page 9, lines 10-15 of the present specification.

The specification further describes the use of fragments of PTHrP as antigens to produce anti-PTHrP antibodies in mammals, such as a rodent (e.g., mouse, rat or

hamster), a rabbit or a monkey. See page 9, line 29 through page 10, line 4 of the specification. Production of anti-PTHrP antibodies from human cells is also described. See page 11, lines 16-26 of the specification. Recombinant anti-PTHrP antibodies are described. See page 11, line 27 through page 12, line 2 of the specification.

Page 14, lines 12-14 of the specification describes the results of Figure 4 of the specification as showing the "effect of the antibodies against the various regions of PTHrP on the proliferation of the tumor cells 786-0 *in vitro* measured by the number of cells… ". Figure 4 describes these "regions" as "N-term", "Region int" and "C-term". The specification further defines these regions as follows (see page 26, line 33 through page 27, line 2 of the specification):

"N-term: anti-PTHrP(1-34) antibody (Bachem) 1.5 µg/ml

Int. region: anti-PTHrP (34-53) antibody (Ab-2, Oncogene) 2 µg/ml

C-term: anti-PTHrP(107-139) antibody (P. Esbrit, Madrid, Espagne) 5 µg/ml" .

One of ordinary skill in the art will appreciate that Figure 4 of the specification describes results of antibodies binding to regions of PTHrP generally, which are described as being applicable to any anti-PTHrP antibody binding the noted region of PTHrP, and are considered a demonstration of the applicants invention.

Figure 6 of the specification similarly describes results relating to anti-PTHrP antibodies which bind to regions "N-term" (i.e., PTHrP(1-34)), "Region Int." (i.e. PTHrP (34-53)), and "C-term" (i.e., PTHrP(107-139)) of PTHrP. The corresponding description of the specification (i.e., page 27, lines 14-23) describes the general applicability of the

results of Figure 6 as representing "the effect of the antibodies directed against the different regions of PTHrP on the proliferation of the UOK-126 tumor cells *in vitro* …".

One of ordinary skill in the art will appreciate that Figure 6 of the specification describes results of antibodies binding to regions of PTHrP generally, which are described as being applicable to any anti-PTHrP antibody binding the noted region of PTHrP, and are considered a demonstration of the applicants invention.

Figure 8 of the specification similarly describes results relating to anti-PTHrP antibodies which bind to regions "N-term" (i.e., PTHrP(1-34)), "Region Int." (i.e. PTHrP (34-53)), and "C-term" (i.e., PTHrP(107-139)) of PTHrP. The corresponding description of the specification (i.e., page 28, lines 1-12) describes the general applicability of the results of Figure 8 as representing "the effect of the antibodies directed against the different regions of PTHrP on the proliferation of the UOK-128 tumor cells *in vitro* …".

One of ordinary skill in the art will appreciate that Figure 8 of the specification describes results of antibodies binding to regions of PTHrP generally, which are described as being applicable to any anti-PTHrP antibody binding the noted region of PTHrP, and are considered a demonstration of the applicants invention.

The applicants submit that one of ordinary skill in the art will appreciate, from the whole of the specification, that the applicants were in possession of the claimed invention, relating to the use of an anti-PTHrP (34-53) antibody. The specification is not limited to the specific Ab-2 anti-PTHrP (34-53) antibody used in the examples.

The Examiner's reliance on In re Smith is misplaced. Consideration of the following in this regard is requested.

The claims under consideration in In re Smith included the following recitation of an organic compound for treating the surface of a pigment to be used in an emulsion coating composition:

> "said organic compound being a monomeric organic compound characterized by at least one non-polar organic hydrophobic group containing at least 8 carbon atoms in a hydrocarbon structure, which group in the form of its monocarboxylic acid" see 173 USPQ 680.

The issue in In re Smith was whether an earlier-filed application provided written description support to antedate a reference. The Smith court summarized from the findings of the Board below which found the earlier filed application failed to

> "mention … the requirement that the coating compound must be a monomer having at least 8 carbon atoms in its hydrophobic moiety, and that more than one polar group was contemplated, all of which is recited in claim 1." See 173 USPQ 682.

The Board rejected the appellants assertions that the following generic disclosure supported the claimed recitation:

> "The treatment of pigments with polar agents is not new per se and can be accomplished by several methods employing a variety of effective compounds. In general these methods involve surface coating the pigment with an oil soluble polar organic compound. Among the polar organic compounds are acidic resins, water soluble resinates, water insoluble metallic resinates, long chain fatty acids, their salts and soaps, benzene carboxylic acid and its salts, naphthenic acids and their soaps and salts, cationic active agents, e.g., alkyl amine salts and quaternary ammonium compounds containing at least 12 carbon atoms in an alkyl group or groups, e.g., lauryl pyridinium bromide, and long chain (at least 12 carbon atoms) fatty acid-containing organic Werner complexes." Id.

The appellants unsuccessfully argued that

> "It is obvious that the surface coating organic compounds recited in the foregoing paragraph are monomeric, have a hydrocarbon structure of at least 8 carbon atoms, except for benzene carboxylic acid which contains six carbon atoms in a hydrocarbon group, and contain at least one carboxy or carboxylate group. If appellant's claims had been drawn more broadly, they would be supported by the parent application. They can be described as subgeneric claims because they delineate the invention more specifically by reciting that the organic material used to coat the pigment is monomeric, contains at least 8 carbon atoms and at least one carboxy or carboxylate group." Id.

The disclosure considered in In re Smith therefore did not contain any written description support for the claimed compounds of "at least 8 carbon atoms" of the claims. Rather, the disclosure considered in In re Smith contained a disclosure of "at least 12 carbon atoms" which the appellants argued supported the lesser inclusive range of the claimed. In affirming the Board, the Smith court likened the facts of Smith to those considered in In re Ahlbrecht (168 USPQ 293 (CCPA 1971)) wherein a disclosure of fluorinated esters having 2-12 CH_2 groups failed to provide written description support for a claim to fluorinated esters having 3-12 CH_2 groups. See 173 USPQ 684. In deciding Smith, the court rejected the "rule" of In re Risse (154 USPQ 1 (CCPA 1967))

> "to the effect that the disclosure of a genus and a species of a subgenus is a sufficient description of the subgenus. We do not now feel that such a rule is consonant with either the letter or spirit of the description requirement of § 112." See 173 USPQ 683.

Unlike the disclosure considered in In re Smith, the present disclosure provides an adequate written description of the general anti-PTHrP (34-53) antibody of the claims, as detailed above. The present facts do not require consideration of whether claims to a range within a broad general disclosure of the specification but outside a less general disclosure or specific disclosure of the specification are supported by the specification, as was the case with In re Smith and In re Ahlbrecht . The present disclosure describes the claimed invention and uses a commercially available product to exemplify the disclosed and claimed invention. One of ordinary skill in the art will appreciate that the applicants described their invention to include use of an anti-PTHrP (34-53) antibody in the claimed method.

Reconsideration and withdrawal of the Section 112, first paragraph "written description", rejection of claims 17-20, 23-26, 31 and 33-35 is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

Respectfully submitted,

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